Screening For Colorectal Cancer

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Colorectal cancer (CRC) is a common, lethal, and preventable disease. It is infrequent before age 40; the incidence rises progressively thereafter to 3.7/1000 per year by age 80 (show figure 1). The lifetime incidence for patients at average risk is 5 percent, with 90 percent of cases occurring after age 50.

CRC is the third leading cause of cancer death, accounting for between 10 and 11 percent of cancer deaths overall; it is third most common in men and women separately [1]. Approximately one in three people who develop CRC die of this disease. (See "Epidemiology and risk factors for colorectal cancer").

Recommendations for CRC screening must take into account several factors, including the effectiveness, safety and convenience of the test, as well as the cost and cost-effectiveness of the screening program. Consideration must also be given to what is best for the individual patient, as well as for clinical policy in general. (See "AGA guideline: Colorectal cancer screening").

All Medicare beneficiaries are entitled to regular colorectal cancer screening. Fecal occult blood tests is reimbursable annually for all patients, flexible sigmoidoscopy is reimbursable once every four years for average risk patients, and screening colonoscopy is reimbursable once every ten years for average risk individuals and once every two years for high risk patients (see below). Barium enema instead of an endoscopic study is reimbursable if the attending physician provides written certification that "...in the case of this particular individual, the estimated potential for the barium enema examination is equal to or greater than the screening potential that has been estimated for the colonoscopy (high risk) or flexible sigmoidoscopy (average risk) for that same individual."

Although screening with fecal occult blood testing and flexible sigmoidoscopy has been shown to reduce mortality from colorectal cancer, screening rates are low. In data analyzed from the 1998 National Health Survey, only 20 to 30 percent of respondents 50 years of age or older reported having had fecal occult blood testing during the preceding two years, and only 5 to 21 percent had a screening endoscopy during the preceding three years [2].

PATHOGENESIS

Adenoma-carcinoma sequence — Most colorectal cancers arise from adenomatous polyps, some of which progress from small (<5 mm) to large polyps (>1.0 cm), and then to dysplasia and cancer. This progression probably takes at least 10 years in most people [3]; the distribution of progression times is not precisely known because polyps are ordinarily removed when they are found. These changes are accompanied by, and probably result from, an accumulation of genetic defects [4].

Some cancers also apparently arise from adenomas that are not polypoid ("flat lesions") [5,6]. In one series of 1000 colonoscopies in England, 36 percent had flat or depressed adenomas that were recognized by distortion of the mucosal pattern and special stains [5]. Large flat adenomas were more likely to contain dysplastic changes than small ones, as is the case for polypoid adenomas. The true proportion and clinical significance of adenomas that are flat is uncertain.

Colorectal polyps are usually either adenomatous or hyperplastic. These lesions cannot be distinguished reliably on gross appearance; biopsy is required for diagnosis (show endoscopy 1).

- Two-thirds of polyps are adenomas. The prevalence of adenomas is 30 percent by age 50, and 50 percent by age 70 (show figure 2). Large adenomatous polyps (>1 cm), the size most likely to progress to cancer, are fortunately less common (3 to 5 percent) than small adenomas [7].

- Hyperplastic polyps account for most of the remaining polyps and are mainly distal. They are generally though not to progress to cancer, although some may [8].

The risk of CRC increases with polyp size, number, and histology (eg, villous worse than tubular architecture). The characteristics of an individual polyp are a marker for the colon as a whole; thus, the polyp examined is representative of the individual's propensity to form polyps and cancer.

The role of polyps as a precursor for cancer, which provides the rationale for endoscopic screening described below, can be illustrated by the benefit of adenoma removal by colonoscopic polypectomy. The National Polyp Study Work Group, for example, followed 1418 patients for a mean of six years in whom complete colonoscopic examination led to the removal of one or more polyps in the colon or rectum [9]. Compared with reference groups with apparently similar risk but in whom polyps were not removed, the incidence of colon cancer was reduced by 88 to 90 percent and by 76 percent when compared with the general population.

RISK AND PROTECTIVE FACTORS FOR COLORECTAL CANCER — The risk of developing colorectal cancer is largely acquired, although genes play a role in some people. The incidence of colorectal cancer, adjusted for age, varies about 15-fold across regions of the world, and people who move from low- to high-risk regions acquire higher rates during their lifetime. Colorectal cancer incidence is 16 percent higher in blacks than whites and substantially lower in Asians, American Indians, and Hispanics [10]. Rates in men are somewhat higher than in women.

Several factors that may be responsible for these differences in risk have been suggested by observational studies and some randomized controlled trials, although none is undisputed (show table 1) [11]. (See "Epidemiology and risk factors for colorectal cancer"). However, while these risk and protective factors modify risk, they do not do so strongly enough to suggest a different approach to screening in individual patients.

Determining risk — Before deciding how to screen, clinicians should decide whether the individual patient is at average or increased risk. A few simple questions are all that is necessary:

- Do you have a family history of colorectal cancer? If so, in first degree relatives, at what age of onset, and how many?

- Have you had a personal history of colorectal cancer or adenomatous polyps?

- Have you had inflammatory bowel disease?

If the answer to all these questions is "no," the patient is considered at average risk. These questions should be asked early in life, and not for the first time when the patient would ordinarily begin screening (at age 50 years) if he or she were at average risk, because screening should begin earlier for patients with increased-risk conditions.

The following are major categories of increased risk that these questions are meant to detect. (See "Epidemiology and risk factors for colorectal cancer", for a more detailed discussion of these risk factors).

Family history — A family history of CRC is present in about 25 percent of cases [12]. Risk is slightly increased if any family member has had CRC. However, clinically important increases in risk are present if CRC occurred in a first-degree relative (eg, parent, sibling, or child), which doubles risk; the risk is as much as six times higher with a larger number of affected relatives and an unusually early age of onset (eg, below age 50 years) [13]. A family history of polyps before age 60 years also increases risk [14]. (See "Family history of colorectal cancer: Risk, pathogenesis, and screening").

Hereditary nonpolyposis colon cancer — Hereditary non-polyposis colon cancer (HNPCC, Lynch Syndrome) is an autosomal dominant condition associated with an approximately 70 percent lifetime risk of developing colorectal cancer. These cancers account for 2 to 5 percent of colorectal cancers, occur relatively early in life (commonly in the 30s and 40s) (show figure 4), and are more likely to occur in the proximal colon. Polyps are no more frequent with this syndrome, although their tendency to develop into cancer is increased. There is an increased risk of other cancers, especially of the female genital track. HNPCC is recognized by a strong family history of colorectal and other cancers and can be confirmed by genetic testing if tissue is available from an affected relative. (See "Screening strategies in patients and families with familial colon cancer syndromes")

Familial adenomatous polyposis — FAP is also a familial cancer, is inherited as an autosomal dominant gene, and accounts for about 1 percent of colorectal cancers. Hundreds to thousands of polyps occur throughout the colon beginning as early as adolescence (show endoscopy 2). Tumors develop beginning in the 20s and nearly 100 percent of people are affected, usually before age 50 (show figure 4). (See "Screening strategies in patients and families with familial colon cancer syndromes").

Prior colorectal cancer or polyps — A prior history of CRC doubles the risk of another primary (metachronous) cancer, apart from the original cancer [15]. A history of adenomatous colorectal polyps also increases the risk of CRC, especially if the polyps are multiple, large, or have villous architecture [16]. (See "Approach to the patient with colonic polyps").

Inflammatory bowel disease — There is a well-documented association between colonic involvement in inflammatory bowel disease (either ulcerative colitis or Crohn's disease) and risk of colorectal cancer if the disease is extensive (pan-colitis) and long-standing (eg, at

least 8 to 10 years). Cancer in these patients develops in areas of dysplasia rather than polyps. (See "Colorectal cancer surveillance in inflammatory bowel disease").

Others — Less common inherited syndromes, Gardner's syndrome (CRC with benign extracolonic tumors) and Turcot's syndrome (CRC with brain tumors), appear to be expressions of known genetic defects, FAP and probably HNPCC. CRC may also be increased in specific clinical situations: ureterocolic anastomoses, acromegaly, and prior pelvic irradiation.

SCREENING TESTS — The pathogenesis of CRC allows two opportunities to prevent cancer: finding and removing polyps to prevent the onset of cancer; and finding and removing early cancers to improve prognosis. In addition, the length of the progression from polyp to cancer affords a wide window of opportunity so that sensitive tests (eg, sigmoidoscopy and colonoscopy) do not need to be repeated yearly, and less sensitive tests (eg, fecal occult blood) performed yearly have a chance of finding lesions missed on earlier screening.

Preventive interventions occur in three phases:

- Screening people without symptoms to identify those with an increased likelihood of disease (eg, because of a positive fecal occult blood test).

- Diagnostic testing to determine whether or not they actually have polyps or cancer, followed by biopsy or excision when necessary.

- Surveillance of high-risk people (typically those in whom a large adenomatous polyp has been found) for new lesions.

The major screening tests now available to detect polyps or CRC are the fecal occult blood test (FOBT), sigmoidoscopy, double-contrast barium enema, and colonoscopy. Digital rectal examination (DRE) is not an effective way of screening for CRC since only 5 to 10 percent of cancers are within reach of the examining finger. However, DRE is part of other screening tests for CRC (sigmoidoscopy, colonoscopy, and barium enema) and may be included in a comprehensive program of preventive health care for other reasons.

Fecal occult blood test — The efficacy of the FOBT has been demonstrated with guaiac-based tests (eg, Hemoccult II). The first clinical trial, published in 1993, randomly assigned 46,551 participants ages 50 to 80 years to screening with FOBT once a year or every two years, or to a control group [17]. Participants who were screened were asked to submit six guaiac-impregnated paper slides with two smears from each of three consecutive stools. They were asked to diet for two days before the test: the diet was characterized by no red meat or turnip/horseradishes (to prevent false positive peroxidase reactions); no gastric irritant drugs (to prevent false positive reactions from gastritis); no vitamin C (to prevent a false negative chemical reaction); and high-fiber foods (to increase stool transit time). Most stools were rehydrated before testing, by adding distilled water to the dry specimen, which increased the sensitivity of the test (and also false positive rate). A positive test was any degree of blue in any sample (show figure 5). Participants who tested positive underwent a diagnostic evaluation, usually with colonoscopy. The following results were noted:

- The 13-year cumulative mortality per 1000 from CRC was reduced in the annual screening group by 33 percent (5.88 versus 8.83 in the control group, number needed to screen 339 for 13 years to prevent one colorectal cancer death).

- Although the sensitivity of a single FOBT is only about 30 percent [18], a program of yearly testing had a sensitivity of about 92 percent.

- Two percent of patients with a positive test had cancer. Thus, for every patient with cancer, 50 patients were subjected to anxiety and further testing (typically colonoscopy).

One criticism of this study was that rehydration of the guaiac test slides greatly increased the incidence of positive results, thereby leading to a large number of colonoscopies and chance detection of cancers. While chance detection certainly occurs, the proportion of all cancers detected in this way is controversial [19,20].

The initial report of this study found that biennial (every two years) FOBT reduced colorectal mortality by only 6 percent [17]. As the follow-up was carried out to 18 years, however, this value increased to 21 percent [21]. These findings are consistent with two other randomized trials of FOBT, which found mortality reductions of 15 to 18 percent associated with biennial screening on nonrehydrated specimens [22,23]. The mortality reduction has continued to increase as screening has continued in one of these cohorts [22,24].

In addition to a reduction in mortality, annual or biennial FOBT also reduces the incidence of colorectal cancer. In the only study of this effect, a statistically significant reduction was found after 18 years of follow-up [25].

Diet during testing, as recommended in the Minnesota study, may not be necessary. A systematic review of three randomized, controlled trials reported that advice to follow a restrictive diet during FOBT screening did not reduce the FOBT positivity rate and very restrictive diets seemed to reduce compliance with screening [26].

FOBT screening has some disadvantages:

- It is not a particularly good test for the detection of polyps, which do not usually bleed
- Mortality is only reduced by one-third or less
- It is necessary to work up many false-positive results

A single stool specimen obtained during a rectal examination is not in itself an adequate screen for colorectal cancer. Only about 5 percent of cancers are within reach of the examining finger, only one specimen is obtained (not six), and there is not good evidence that this approach is beneficial. On the other hand, a positive test for occult blood on a specimen obtained during rectal examination should not be ignored. (See "Evaluation of occult and obscure gastrointestinal bleeding" for a discussion of issues related to performance of FOBT, including a discussion of the types of FOBT and slide rehydration.)

Sigmoidoscopy — The 60 cm sigmoidoscope can reach to the splenic flexure and so directly identify about one-half of colonic lesions (either cancers or polyps). An additional 20 percent of neoplasms are found if abnormal sigmoidoscopies are followed by colonoscopy or barium enema.

Primary care physicians and nurse practitioners/physician assistants can become proficient in the technique of sigmoidoscopy if properly trained. The patient preparation is minimal (typically with Fleets enemas the night before and a few hours before the procedure), and the procedure may be performed in the physician's office without the need for patient sedation since it generally only causes mild cramping. Perforation rates with a trained operator are about 1 to 2 per 100,000, and mortality is rare.

There is evidence from well-designed, case-control studies that sigmoidoscopy reduces CRC mortality by two-thirds in the part of the bowel examined [27-29], about half of the large bowel [29]. Small adenomas can be biopsied during the procedure. However, excision of larger lesions (>1 cm) is usually done during a subsequent colonoscopy.

There is general agreement that when screening sigmoidoscopy discloses a large adenoma (>1.0 cm), adenomas of any size with tubulovillous or villous histology, or multiple adenomas, there is a substantially increased risk of advanced neoplasia in the proximal colon [30], and sigmoidoscopy should be followed by colonoscopy. It is less clear whether patients found to have a single, small (<0.6 cm) tubular adenoma of the distal colon should undergo more extensive examination or simply return to average-risk screening. Three kinds of evidence bear upon this question:

- Advanced proximal lesions are not uncommon in patients with distal adenomas; several studies have reported rates ranging from 0 to 10 percent [31-34]. The variation can probably be explained by somewhat different inclusion criteria (such as screening versus diagnostic sigmoidoscopies, average- or high-risk patients) and statistical imprecision of the results. As an example, one study found advanced proximal neoplasms in 4 of 41 patients with an index tubular adenoma of 5 mm or less; the rate, 10 percent, has a 95 percent confidence interval of 1 to 19 percent [35]. All reported estimates have overlapping confidence intervals in the region of 1 to 4 percent [36].

- People with a single, small, distal tubular adenomas are at relatively low risk for subsequent colon cancer. In a cohort study in London, 1618 patients referred for colorectal symptoms were found to have rectosigmoid adenomas, and underwent polypectomy [30]. These patients did not undergo colonoscopy and were followed up for a mean of 14 years without surveillance (before the colonoscopy era). Patients with only a single small tubular adenoma had a colon cancer incidence that was 0.5 that of the general population.

- Advanced proximal lesions, while not uncommon, may be no more likely in people with tubular adenomas than in those with no adenoma. In one study, 2972 asymptomatic patients age 50 years or older underwent colonoscopy as follow-up to a screening sigmoidoscopy [37]. The prevalence of advanced proximal neoplasia was 5.3 percent in patients with no tubular adenoma, 5.5 percent in those with tubular adenomas <1.0 cm, and 5.6 percent in those with tubular adenomas ≥1.0 cm. In comparison, 12.1 percent of patients with distal tubulovillous or villous adenomas had advanced proximal neoplasia.

Opinions regarding follow-up of small tubular adenomas are also based upon different value judgments applied to the same facts, with referral colonoscopists in general believing that follow-up colonoscopy is indicated. Furthermore, the threshold for doing colonoscopy is colored by the growing belief in colonoscopy as a reasonable screening option in its own right.

Until a consensus emerges, it is reasonable for clinicians to either follow-up patients with small distal tubular adenomas with colonoscopy or to treat them as average-risk patients [38]. My practice is to recommend colonoscopy to all patients with distal adenomas, except those with single, small, tubular adenomas with whom I discuss the possibility of proximal pathology but the marginal benefit of further investigation.

FOBT plus sigmoidoscopy — There are theoretical reasons for combining FOBT and sigmoidoscopy. FOBT may be less sensitive for the detection of CRC in the distal bowel, perhaps because of sampling error when bleeding from the neoplasm is less mixed with the rest of the stool, while the distal one-half of the bowel can be carefully examined for both polyps and cancer with sigmoidoscopy. The main direct evidence supporting this combined practice is a nonrandomized trial that demonstrated a 43 percent reduction in CRC mortality in patients receiving both tests compared with sigmoidoscopy alone [18]. In addition, a case-control study showed that FOBT reduced CRC mortality even after controlling for patients who had sigmoidoscopy [39].

On the other hand, FOBT plus sigmoidoscopy misses a number of invasive cancers. In a study of 2885 asymptomatic men (ages 50 to 75 years), one time screening with FOBT (with rehydration of slides) and sigmoidoscopy failed to detect advanced colonic neoplasia in 24 percent of patients [40]. Sensitivity may be improved with repeated screening at suggested intervals.

Double-contrast barium enema — DCBE is more sensitive and specific than single column barium enema. It is therefore the radiologic procedure of choice despite the fact that it is somewhat more difficult to perform than a single column study and is more expensive. Patients must undergo bowel preparation with a saline cathartic. Sedation is not ordinarily given. Patients experience some cramping during the procedure, but can return to work after the examination.

The best available evidence suggests that DCBE detects only about half of adenomas larger than 1.0 cm and 39 percent of all polyps [41]. Abnormalities must be followed by colonoscopy for biopsy or excision. False positive results can result from retained stool, air, and other causes of mucosal irregularity. Potential advantages of DCBE are that it can be used to examine the entire colon and rectum, and it is relatively safe.

There are no studies evaluating the effectiveness of DCBE in the prevention of CRC deaths. It can be reasoned that DCBE is effective since it identifies lesions better than FOBT and nearly as well as colonoscopy, two tests which have been shown to lower CRC mortality. DCBE may perform less well in the rectosigmoid than in the rest of the colon, but this hypothesis has not been rigorously tested. Adding sigmoidoscopy to DCBE probably detects more lesions; however, this combination is difficult to arrange and it is unclear if the gain in sensitivity is clinically important.

Colonoscopy — There is a strong biologic argument that colonoscopy can prevent CRC deaths; it can find most polyps and nearly all large polyps and cancers. A recent study assessed the sensitivity of colonoscopy for detection of polyps by performing colonoscopy twice in one day by different but experienced endoscopists in 183 patients: the initial procedure missed 27 percent of adenomas <5 mm in size, 13 percent of adenomas 6 to 9 mm in size, but only 6 percent of adenomas >10 mm in size [42].

Colonoscopy has the added benefit that lesions can be removed during the same procedure. In addition, colonoscopy finds a significant number of proximal lesions that would otherwise

be missed by performing sigmoidoscopy [43,44]. In one study of screening colonoscopy in 2000 asymptomatic individuals, for example, 62 percent of patients with advanced neoplasms in the proximal colon had either no distal lesions or only hyperplastic polyps that would not have warranted follow-up colonoscopy [43].

As noted above, a study of patients with polyps (not a screened population) in which the colon was cleared of polyps by colonoscopy showed a large reduction in mortality (76 to 90 percent) compared with patients who did not have polyps removed or compared with people in the general population [9]. However, there is no direct evidence that colonoscopy reduces CRC mortality in people without symptoms or known polyps. Nevertheless, studies showing that sigmoidoscopy reduces CRC deaths from cancers in the part of the bowel examined provide indirect evidence that the colonoscope, in effect a longer sigmoidoscope, should also be effective [27-29].

One disadvantage of screening colonoscopy is the risk; the rate of major complications (perforation and major bleeding) is about 1 per 1000 procedures. It also is expensive. Colonoscopy requires careful bowel preparation with a saline cathartic. Patients usually receive conscious sedation and are comfortable during the procedure. However, because of the sedation, they must be accompanied home after the test, and they usually cannot return directly to their usual activities.

Colonoscopy has become an increasingly popular choice for screening. The American College of Gastroenterology now considers colonoscopy the "preferred" screening test [45], but other expert groups simply list it as an option.

Comparison of tests and cost-effectiveness — Many factors are weighed by patients and physicians in trying to determine the optimal screening tool, including strength of the evidence of effectiveness; magnitude of the effect (eg, reduction in incidence or mortality from CRC); safety; convenience; cost; and cost per year of life saved (cost-effectiveness). The options for screening differ substantially in many of these areas (show table 2A-2B) [38].

The costs of screening vary substantially from test to test. As an example, in one model FOBT was $38 and screening colonoscopy $1012 [46]. These costs are borne up front, whereas the reduction in mortality and incidence occur after several years. Nevertheless, cost-effectiveness models taking the societal perspective have found that all current options for screening are "cost-effective," relative to other accepted screening tests [46-48]. Costs rise steeply with shorter intervals of screening, with much smaller increases in effectiveness.

Analyses have differed in which test has the most favorable cost-effectiveness ratio. One model found that the FOBT/sigmoidoscopy combination was most effective and its cost-effectiveness was about $36/000 per year of life saved [46]. Another found that colonoscopy was more cost-effective than FOBT screening if compliance were less than perfect [47]. There is no compelling reason to choose one option over the others on the basis of cost-effectiveness alone [48].

In addition to studies of cost-effectiveness, patient preferences have been evaluated. As an example, in a study of 217 patients in a general medicine clinic, five options for colorectal cancer screening were offered, including FOBT annually, flexible sigmoidoscopy every five years, combination of the last two, colonoscopy every ten years, or double contrast barium enema every five to ten years [49]. Patients were given information about each choice,

including frequency, discomfort, complications, inconvenience (eg, preparation), time, accuracy, and need for further testing. Over 80 percent of patients preferred either FOBT (43 percent) or colonoscopy (40 percent).

EMERGING TESTS — New screening tests are being developed but their performance has not yet been sufficiently studied to be included as screening options.

Virtual colonoscopy — Virtual colonoscopy, a computer enhanced spiral CT scan after bowel preparation and air insufflation, allows visualization of the entire colonic mucosa. (See "Virtual colonoscopy"). The utility of this technique for screening was evaluated in a prospective study of 100 patients at high risk for colorectal cancer [50]. All patients underwent virtual colonoscopy, immediately followed by conventional colonoscopy. The entire colon was clearly seen in 87 and 89 cases, respectively. Virtual colonoscopy identified all 3 cancers, 20 of 22 polyps (91 percent) that were 10 mm or greater in diameter, 33 of 40 (82 percent) that were 6 to 9 mm in diameter, and 29 of 53 (55 percent) that were 5 mm or smaller. Another study found comparable results [51].

However, despite the relative success at identifying polyps 6 mm and larger, barriers to use of virtual colonoscopy as a screening tool include the need to undergo a full cleansing procedure, uncomfortable gas insufflation of the colon, cost, large number of false positives, and the lack of widespread availability and expertise in interpretation of results. A number of patients find this technique to be more painful and embarrassing than conventional colonoscopy.

Newer tests for fecal blood — Several new tests for FOBT have been developed. Hemoccult Sensa R is more sensitive than Hemoccult II. HemeSelect R, an immunochemical test for hemoglobin, is more specific because it responds only to hemoglobin and not to upper gastrointestinal bleeding (since the blood is digested in transit).

One study tested over 8000 patients with Hemoccult II, Hemoccult II Sensa, HemeSelect, or a combination of Hemoccult II Sensa followed by HemeSelect in cases with positive tests [52]. The sensitivity of the tests for detecting carcinoma was lowest with Hemoccult II (37.1 percent), intermediate with the combination test (65.6 percent) and with HemeSelect (68.8 percent), and highest with Hemoccult II Sensa (79.4 percent). The respective specificities for detecting carcinoma were 97.7, 97.3, 94.4, and 86.7 percent. Thus, Hemoccult II Sensa screening followed by HemeSelect for positive tests was an improvement over Hemoccult II or the other tests alone.

Fecal genetic abnormalities — DNA from colonic neoplasms is shed in the stool and can be analyzed for the set of genetic defects typically acquired during carcinogenesis. In one study, a panel of selected DNA alterations detected neoplasms with a sensitivity of 91 percent for cancer and 82 percent for adenomas, with a specificity of 93 percent [53]. A second report found that a combination of molecular tests involving only three genetic mutations detected 71 percent of patients with colorectal cancer, although most of the cancers were advanced and the patients were symptomatic [54].

RECOMMENDATIONS FOR AVERAGE RISK PEOPLE — Expert groups have recommended colorectal cancer screening programs that resemble each other in most respects. They recommend four options and their combinations: FOBT, sigmoidoscopy, FOBT + sigmoidoscopy, double contrast barium enema, and colonoscopy [38,55].

In practice, FOBT is the most commonly used screening test, followed by sigmoidoscopy; screening colonoscopy is gaining in popularity [56]. The American College of Gastroenterology recommends screening colonoscopy over other options [45] and Medicare now pays for screening colonoscopy in average risk people. Barium enema has not been a very popular screening option and seems to be waning in recent years.

The first step in screening is to determine whether the patient is at average or increased risk and, if the latter, the specific reason. If the patient is found to be at average risk, we support the following recommendations, prepared by a multi-disciplinary panel convened by the AHCPR and sponsored by a consortium of gastroenterology societies (show figure 6) [38].

- Offer screening beginning at age 50 years. This recommendation is based upon the rapid rise in colorectal cancer incidence after age 50, and is supported by studies that have found that colonoscopic detection of colorectal cancer is uncommon in asymptomatic people under the age of 50 [57].

- The patient and doctor should decide together which of a set of reasonable options for screening is best for him or her, armed with information about the effectiveness, convenience, safety, and cost of each test.

The following options are supported by strong evidence of effectiveness:

- Offer fecal occult blood screening each year.

- Offer screening sigmoidoscopy with flexible sigmoidoscopy every five years. All polyps should be biopsied. If adenomatous polyps or cancer are found, the patient should be offered colonoscopy to remove polyps, treat limited cancers definitively, and examine the entire colon and rectum for synchronous neoplasms. Patients with tubular adenomas smaller than 0.5 cm should decide with their physician whether to undergo colonoscopy.

The individual components of the following strategy are supported by strong evidence of effectiveness, but the additional value of combining the two, while theoretically present, is not well established by research evidence:

- Offer screening that includes both FOBT and sigmoidoscopy (as described above) together.

The following options seem to be effective when all evidence is considered, but are not supported by direct evidence (from randomized trials, nonrandomized trials, or case-control studies) that they reduce mortality from colorectal cancer:

- Offer double-contrast barium enema every 5 to 10 years.

- Offer colonoscopy every 10 years.

Although all of these options are reasonable, they differ substantially in ways that matter to patients (such as effectiveness, safety, convenience, and cost) and none is best on all dimensions. Thus, patients and their clinicians should decide which is best for them.

RECOMMENDATIONS FOR PEOPLE AT INCREASED RISK — Patients at increased risk for CRC should be screened differently from those at average risk, depending upon the specific reason for the increased risk. The evidence for how they should be screened, however, is much weaker than for average risk patients since there are few controlled comparisons. Thus, guidelines are based mainly upon arguments relating to knowledge of the biology of CRC:

- If the patient is at risk for earlier onset CRC (eg, first degree relative with onset of CRC before age 50), screening should begin earlier.

- If the patient is at risk for more rapid progression of disease, screening should be performed more frequently.

- If the patient is at risk for more proximal lesions (eg, HNPCC), screening should be performed with colonoscopy or DCBE.

- If the patient is at risk for a greatly increased incidence of disease (eg, FAP), more sensitive tests should be used (eg, colonoscopy or DCBE).

The following are recommendations for screening people at increased risk for colorectal cancer (show figure 6) [38].

Patients with a close relative (sibling, parent, or child) who has had colorectal cancer or an adenomatous polyp — These patients should be offered the same options as average risk patients, but beginning at age 40 rather than 50. If the close relative was diagnosed with colorectal cancer before the age of 55 or with an adenomatous polyp before age 60, special efforts should be made to assure that screening takes place. In practice, many of these patients prefer periodic complete evaluation of the colon with colonoscopy, although there are no studies that have shown that more aggressive screening is more effective in this situation. (See "Family history of colorectal cancer: Risk, pathogenesis, and screening").

Patients with a family history of FAP — These patients should receive genetic counseling and consider genetic testing to see if they are gene carriers. A negative genetic test result rules out FAP only if an affected family member has an identified mutation. Gene carriers or indeterminate cases should be offered flexible sigmoidoscopy every 12 months beginning at puberty to see if they are expressing the gene; sigmoidoscopic surveillance is sufficient since adenomatous polyps occur throughout the bowel in this disease. (See "Screening strategies in patients and families with familial colon cancer syndromes").

If multiple adenomatous polyps are present, the patient should begin to consider when to undergo colectomy given the almost 100 percent lifetime risk of colon cancer in this disease. Total proctocolectomy is the only feasible way to prevent the development of cancer and should be performed as soon as the procedure is acceptable to the patient.

Patients with a family history of HNPCC — Patients with a family history of colorectal cancer in multiple close relatives and across generations, particularly if cancers occur at a young age, should receive genetic counseling and consider genetic testing for HNPCC. They should be offered an examination of the entire colon every one to two years starting between the ages of 20 and 30, and every year after the age of 40; sigmoidoscopic

examination is insufficient because the cancers tend to be proximal. (See "Screening strategies in patients and families with familial colon cancer syndromes").

There is no direct evidence on which to base a precise screening interval. However, the interval between screening examinations should be shorter than for average risk patients because polyps may progress rapidly to cancer in these patients, and the probability of cancer and adenomatous polyps being present at each examination is so high that the risk of missing a clinically important lesion is substantial.

SURVEILLANCE — Once polyps have been identified by screening, the patient should be entered in a colonoscopy surveillance program. Clearing the colon of polyps and keeping it clear can reduce mortality by as much as 90 percent [9].

Patients in whom large (>1 cm diameter) or multiple adenomatous polyps are found and removed at colonoscopy should have an examination of the colon three years after the initial examination; this interval has been shown to be as good as one year in a randomized trial [58]. The evidence base for the interval of subsequent follow-up is not as strong and depends upon the nature of their polyps. If only a small tubular adenoma is found, for example, the interval can be 6 to 10 or more years; in contrast, the interval should be much shorter after removal of a large villous adenoma. A large part of the feasibility and cost-effectiveness of colonoscopic surveillance depends upon lengthening the interval between procedures as much as possible when the risk of new advanced lesions is low. (See "Approach to the patient with colonic polyps").

Patients with a history of colorectal cancer — Recommendations for colorectal cancer surveillance in patients with a history of colorectal cancer have been proposed by the American Society of Clinical Oncology (ASCO) [59]. Patients should have full visualization of the colon at the time of diagnosis to exclude synchronous cancers and polyps. A complete examination can be performed after surgery in patients in whom full examination could not be performed preoperatively. A subsequent colonoscopy should be performed every three to five years to detect new cancers or polyps (show table 3). (See "Surveillance after colorectal cancer resection").

Other surveillance recommendations proposed by ASCO include:

- Carcinoembryonic antigen (CEA) testing every two to three months for ≥2 years in patients with stage II or III disease in whom resection of liver metastases would be clinically indicated

- A history and physical examination every three to six months for the first three years and annually thereafter

Patients with inflammatory bowel disease — In patients with long-standing extensive inflammatory bowel disease, surveillance colonoscopy looking for dysplasia as a marker of colorectal cancer risk should be considered along with the extent and duration of the disease as a guide to when or if colectomy should be considered. It is common practice to perform surveillance colonoscopy every one to two years beginning after eight years of disease in patients with pancolitis, or after 15 years in those with colitis involving only the left colon. However, there is no direct evidence that this practice reduces colorectal cancer mortality, nor is there evidence that it is more effective than basing colectomy solely upon the extent and duration of disease. (See "Colorectal cancer surveillance in inflammatory bowel disease").

INFORMATION FOR PATIENTS — Some useful sources of information for patients include:

- Centers for Disease Control (www.cdc.gov/cancer/screenforlife
- American Cancer Society (www.cancer.org)
- National Cancer Institute PDQ treatment information for patients (www.cancernet.nci.nih.gov/clinpdq/pif/Colon_cancer_Patient.html)
- The colorectal cancer educational material provides links to other sites (www.mediconsult.com/noframes/colon/shareware/content.html)

(See "Patient information: Screening for colon cancer").

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Summary of the Characteristics of Each Screening Test for Colorectal Cancer Discussed in AGA Guideline†

Screening test	Overall performance	Complexity	Potential effectiveness	Evidence of effectiveness	Screening test risk
Fecal occult blood test	Intermediate for cancers, low for polyps	Lowest	Lowest	Strongest	Lowest
Flexible sigmoidoscopy	High for up to half of the colon	Intermediate	Intermediate	Intermediate	Intermediate
FOBT + flexible sigmoidoscopy	Same as flexible sigmoidoscopy and FOBT	Intermediate	Intermediate	Intermediate	Intermediate
Double contrast barium enema	High	High	High	Weakest	Intermediate
Colonoscopy	Highest	Highest	Highest	Weakest	Highest

NOTE. The costs of the screening tests themselves, also an important characteristic, vary, but the costs of the screening strategies (lifetime programs of screening and follow-up of abnormal test results) are comparable. Complexity involves patient preparation, inconvenience, facilities and equipment needed, and patient discomfort.

†Adapted from Winawer, SW, Fletcher, RH, Mille, L, et al AGA guidelines: Colorectal cancer screening: Clinical guidelines and rationale. Gastroenterology 1997; 112: 594.

Major Complication Rates of Screening Tests†

Screening test	Complication rate (perforation and hemorrhage)	Death
Barium enema	1/10,000	1/50,000
Sigmoidoscopy	1-2/10,000	<1/10,000
Diagnostic colonoscopy	1-3/1,000††	1-3/10,000

†The decision analysis used more conservative (eg, worst case) estimates of complication rates. Adapted from Winawer, SJ, Fletcher, RH, Miller, L, et al. Gastroenterology 1997; 112:594.
††Major complications are more frequent if polypectomy is performed.